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Clinical presentation and outcomes in elderly patients with symptomatic isolated subsegmental pulmonary embolism

Running head: Subsegmental Pulmonary Embolism in Elderly People

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ABSTRACT

Objectives: Data are limited on clinical presentation and outcomes in elderly patients with acute symptomatic isolated subsegmental pulmonary embolism (SSPE). We compared clinical presentation, risk factors, processes of care, and outcomes between elderly patients with SSPE and patients with more proximal pulmonary embolism (PE).

Methods: We prospectively followed 578 patients aged ≥65 years with acute symptomatic isolated SSPE or proximal PE in a multicentre Swiss cohort study. We compared quality of life at three months using the PEmb-QoL, and examined the independent association between localization of PE and clinical outcomes (recurrent venous thromboembolism [VTE], overall mortality) using regression models with adjustment for potential confounders.

Results: Overall, 11% of patients had isolated SSPE. Patients with SSPE were less likely to have a pulse ≥110/min (3% vs. 13%), but more likely to have active cancer (28% vs. 15%) and to receive outpatient care (11% vs. 4%) than patients with proximal PE. Virtually all patients (98%) with SSPE received anticoagulants. Quality of life did not differ between the groups at 3 months. No patient with SSPE vs. seven patients with proximal PE died from the index PE event. No significant difference was observed for the 3-year cumulative incidence of recurrent VTE (7% vs. 12%) and death (29% vs. 20%). After adjustment, SSPE was not associated with a lower risk of clinical outcomes than proximal PE.

Conclusions: Clinical presentation and incidences of adverse outcomes did not differ significantly between elderly patients with SSPE or proximal PE, although the power to detect differences might have been limited given the small number of events. Thus, our study does not provide evidence that unselected, elderly patients with SSPE have a more benign clinical course.

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Keywords: Aged; Anticoagulants; Patient outcome assessment; Pulmonary embolism; Venous thromboembolism

Abbreviations:

AC	Anticoagulation
BP	Blood pressure
CI	Confidence interval
CT(PA)	Computed tomography (pulmonary angiography)
DOAC	Direct oral anticoagulant
DVT	Deep vein thrombosis
Hs-cTNT	High-sensitivity cardiac troponin T
INR	International Normalized Ratio
IQR	Interquartile range
NSAID	Non-steroidal anti-inflammatory drugs
PEmb-QoL	Pulmonary Embolism Quality of Life
PESI	Pulmonary Embolism Severity Index
(S)HR	(Sub-)hazard ratios
(SS)PE	(Subsegmental) pulmonary embolism
SWITCO65+	Swiss cohort of elderly patients with venous thromboembolism
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

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INTRODUCTION

Acute isolated subsegmental pulmonary embolism (SSPE), defined as pulmonary embolism (PE) that occurs in one or more subsegmental pulmonary artery branches but no larger order of vessels [1], is increasingly detected with the technological advance in computed tomography pulmonary angiography (CTPA) [2]. SSPE represents 7–36% of cases of PE [3-6], and the vast majority of patients with SSPE receive anticoagulant treatment [6]. However, the diagnosis and treatment of SSPE pose several challenges. Given a positive predictive value of as low as 25% for SSPE with CTPA and an only fair interobserver agreement between radiologists [7, 8], many cases of SSPE may represent false-positive results (e.g., artefacts) rather than true PE [9]. It has also been hypothesized that the lung may act as a natural filter to protect systemic circulation and therefore, SSPE may represent a normal finding [10]. Moreover, direct and indirect evidence from retro- and prospective studies suggests that SSPE may have a less severe clinical presentation and a lower risk of venous thromboembolism (VTE) recurrence and PE-related death than more proximal PE [3, 4, 11], and that withholding anticoagulation in selected low-risk patients with SSPE (i.e., those without concomitant proximal deep vein thrombosis [DVT]) could be safe [4, 12, 13]. In contrast, another study found that patients with SSPE mimic those with more proximal PE in regard to their risk profile and clinical outcomes [5].

Although the majority of VTE cases occur in patients aged ≥65 years [14], little is known about the clinical presentation, VTE risk factors, processes of care, and outcomes in elderly patients with isolated SSPE. Previous studies on SSPE were mostly performed in patients aged <70 years [12], and whether their results can be generalized to the elderly remains unknown. To fill this gap of knowledge, we compared the clinical presentation, VTE risk factors, processes of care, and outcomes between elderly patients with isolated SSPE and those with more proximal PE. Given

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the diagnostic uncertainty and doubtful clinical relevance of SSPE, we hypothesized that elderly patients with SSPE are less likely to experience adverse outcomes compared to patients with more proximal PE.

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METHODS

Cohort sample

The study was conducted as part of the Swiss cohort of elderly patients with VTE (SWITCO65+) [15]. In this multicentre prospective cohort study, consecutive in- and outpatients aged ≥65 years with acute symptomatic, objectively confirmed VTE were enrolled at nine Swiss hospitals between September 2009 and March 2012 and followed until December 2013. Exclusion criteria comprised the inability to provide informed consent (i.e., severe dementia), impracticable follow-up due to terminal illness or place of living too far away from the study centre, insufficient German or French speaking ability, venous thromboses other than lower limb DVT or PE (e.g., catheter-related thrombosis), or prior enrolment in the cohort. The detailed study methods, including eligibility criteria, were published previously [15]. The study was approved by the ethics committees at each participating site.

For the present study, we considered all patients from the original cohort who had an initial diagnosis of symptomatic PE (i.e., acute chest pain, new or worsening dyspnoea, or syncope) detected by an objective imaging exam, such as spiral CTPA, pulmonary angiography, or high-probability ventilation/perfusion scintigraphy [15]. Patients who had a diagnosis of SSPE without the presence of any more proximal PEs based on the interpretation of on-site radiologists were considered to have isolated SSPE. Because proximal DVT is associated with adverse outcomes in patients with PE [16], we excluded patients with isolated SSPE who had concomitant proximal DVT.

Data collection

For all enrolled patients, trained study nurses prospectively collected information about baseline demographics such as age, sex, localization of the index PE (SSPE vs. more proximal PE), VTE risk factors (active cancer, immobilisation,

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major surgery, oestrogen therapy, and history of VTE), comorbidities (chronic heart failure, chronic lung disease, and history of major bleeding), clinical symptoms and signs of VTE (acute chest pain, new or worsening dyspnoea, new unilateral leg pain or leg swelling, pulse, systolic blood pressure, respiratory rate, body temperature, mental status, arterial oxygen saturation), and routine laboratory findings (haemoglobin, platelet count). The revised Geneva score as a clinical decision rule to assess the risk of PE in patients with suspected PE and the Pulmonary Embolism Severity Index (PESI) to estimate the 30-day overall mortality risk were calculated retrospectively [17, 18]. We further assessed the therapy initiated within one month of the index PE (vitamin K antagonists [VKA], parenteral anticoagulation, no anticoagulation, thrombolysis, inferior vena cava filter), concomitant treatments (antiplatelet and non-steroidal anti-inflammatory drugs), and the initial site of management (in- or outpatient setting). Type and duration of anticoagulation as well as the site of initial management was left to the discretion of the managing physicians.

Study outcomes

The primary outcome was the recurrence of symptomatic VTE during the follow-up period, defined as a new or recurrent, fatal or non-fatal, symptomatic, and objectively confirmed PE and/or DVT, as previously described [15]. Secondary outcomes included overall mortality, PE-related mortality (defined as deaths certainly or possibly related to PE), and PE-specific quality of life based on the Pulmonary Embolism Quality of Life (PEmb-QoL) questionnaire. The PEmb-QoL questionnaire is an instrument with six dimensions (frequency of complaints, limitations in activities of daily living, work-related problems, social limitations, intensity of complaints, and emotional complaints) and 40 items to measure quality of life in patients with PE reflecting the patients' perspective over the past four weeks [19, 20]. The summary

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score ranges between zero (best quality of life) and 100 (worst quality of life) [21, 22] with an assumed minimal clinically important difference of 15 points [23]. We used the validated French and German versions of the PEmb-QoL [21, 22]. The tertiary outcome was the duration and quality of oral anticoagulation with VKAs, the latter expressed as the percentage of time spent in a given International Normalized Ratio [INR] range (<2.0, 2.0–3.0, >3.0) according to Rosendaal's method [24]. Patients who did not take VKA, had less than two INR measurements, or died within the first six months, were excluded from analyses of anticoagulation.

Follow-up included one telephone interview and two face-to-face evaluations during the first year of study participation and then semi-annual contacts, alternating between face-to-face evaluations and telephone calls, as well as periodic hospital chart reviews. As part of the follow-up interviews/visits, study nurses obtained information about the date and localization of VTE recurrence, death, and PE-specific quality of life. We also collected INR values throughout follow-up. A committee of 3 independent, blinded clinical experts adjudicated all outcomes. They classified the cause of all deaths as definitely due to PE (i.e., confirmed by autopsy or death following a clinically severe PE), possibly related to PE (i.e., death in a patient who died suddenly without any other explanation), or due to another cause. PE-related death was defined as death definitely or possibly related to recurrent PE. Final assignments were based on the full consensus of this committee.

Statistical analyses

We compared baseline characteristics, mean PEmb-QoL summary scores at three months, duration of anticoagulation, and the percentage of time spent in a given INR range (<2.0, 2.0–3.0, >3.0) between patients with isolated SSPE and those with more proximal PE using chi-square or Wilcoxon rank-sum tests as appropriate. A P-

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value <0.05 was considered statistically significant. Recurrent VTE, overall mortality, and PE-related mortality in patients with SSPE vs. those with more proximal PE were compared at three months and over the entire follow-up period. We additionally compared PE-related deaths that occurred during the index hospitalization to assess mortality due to the index PE. The 3-year cumulative incidences of recurrent VTE events by localization of PE were compared using the Aalen-Johansen estimator and the Gray test, which both account for the competing risk of death [25, 26]. For mortality, we used the Kaplan-Meier estimator and the log-rank test.

We explored the associations between SSPE and the time to a first recurrent VTE using competing risk regression [27], accounting for non-PE-related death as a competing event. The method yields sub-hazard ratios (SHR) with corresponding 95% confidence intervals (CIs). We adjusted the models for risk factors previously shown to be associated with recurrent VTE (age, sex, active cancer, history of VTE) [28-32], as well as periods of anticoagulation as a time-varying covariate. For overall mortality, we used Cox-regression with robust standard errors, adjusting for age, sex, active cancer, chronic lung disease, heart failure [18, 33, 34], and periods of anticoagulation as a time-varying covariate. Because the diagnosis of SSPE based on ventilation/perfusion scanning is not standardized, we excluded all non-CTPA-based PE cases in a sensitivity analysis. We assumed missing values in adjustment variables to be normal or absent as done previously [18, 35]. All analyses were done using Stata 15 (Stata Corporation, College Station, Texas).

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RESULTS

Study sample

Of 1863 screened patients with symptomatic VTE, we excluded 462 who had ≥1 exclusion criterion and 398 who did not consent to participate (Fig. 1). After the exclusion of another 425 patients who withdrew from the study within one day of enrolment, refused the use of their data, had objectively confirmed DVT only, or had concomitant proximal DVT, our final sample comprised 578 patients. Of these, 64 had isolated SSPE (11%) and 514 more proximal PE.

The median age was 75 years (interquartile range [IQR] 70–81 years) and 53% of patients were men. Patients with isolated SSPE were more likely to have active cancer (28% vs. 15%, P=0.01) and less often to have a pulse ≥110/min. (3% vs. 13%, P=0.02) than patients with proximal PE (Table 1). The revised Geneva score, cardiac biomarker levels, and the short-term mortality risk based on the PESI were comparable between the two groups.

All but four patients (1 with isolated SSPE, 3 with more proximal PE) were treated with initial anticoagulants (VKA or parenteral anticoagulation), but the initiation of VKA therapy was less frequent in patients with isolated SSPE than in patients with more proximal PE (80% vs. 91%, P=0.01; Table 1). Patients with isolated SSPE were more often treated as outpatients (11% vs. 4%, P=0.02). The median follow-up period was 30 months (IQR 18–36 months).

Primary outcome (recurrence of VTE)

The risk of recurrent VTE at three months and over the entire follow-up period (Table 2), and the 3-year cumulative incidence of recurrent VTE (Fig. 2a) did not differ significantly between patients with SSPE and those with more proximal PE. After adjustment, there was no statistically significant difference in recurrent VTE during

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follow-up between the two groups (SHR 0.64, 95%CI: 0.25–1.62; Table 3). Excluding the 58 patients in whom PE-diagnosis was not based on CTPA in a sensitivity analysis did not substantially change the results (SHR 0.57, 95%CI: 0.20–1.62; Table 3).

Secondary outcomes (overall mortality, PE-related mortality, PE-specific quality of life)

Of the 18 patients with isolated SSPE who died during follow-up, two died from possible recurrent PE (sudden death without any other explanation) on day 82 and 1120 of follow-up. Of the 97 patients with proximal PE who died during follow-up, 21 patients died from definite (n=6) or possible PE (n=15). Of these, seven died from PE during the hospitalization for index PE. Overall mortality and mortality definitely or possibly related to PE during the index hospitalization, at three months, and over the entire follow-up period (Table 2), as well as the 3-year cumulative incidence of overall mortality (Fig. 2b), did not differ significantly between patients with isolated SSPE and those with more proximal PE. After adjustment, the risk of overall mortality did not differ between the two groups (hazard ratio [HR] 1.12, 95%CI: 0.64–1.96; Table 3). After the exclusion of the 58 patients without a CTPA-based PE diagnosis, mortality did not differ by PE localization (HR 1.34, 95%CI: 0.71–2.53, Table 3).

PE-specific quality of life, expressed as the PEmb-QoL summary score at three months following the index PE, was similar in patients with isolated SSPE and those with more proximal PE (median 22.8 vs. 22.9 points; P=0.70).

Tertiary outcomes (duration and quality of anticoagulation)

The median duration of initial anticoagulation did not differ between patients with SSPE and those with more proximal PE (10.7 [IQR 6.1–24.1] vs. 12.3 [6.3–28.7]

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261 months; P=0.34; Table 4). The quality of anticoagulation, expressed as the time in a

262 given INR range, was also comparable between the PE groups (Table 5).

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DISCUSSION

In our prospective study of elderly patients with acute symptomatic PE, patients with isolated SSPE did not differ significantly in their clinical presentation, but had a higher prevalence of cancer, and a higher probability of receiving outpatient treatment than patients with more proximal PE. The PESI risk classes, the duration and quality of anticoagulation, and short- and long-term clinical outcomes did not differ significantly between the two groups, although the power to detect differences might have been limited given the small number of events. To our knowledge, this is the first study exploring differences between SSPE and proximal PE in the elderly.

Whether isolated SSPE is clinically more benign than more proximal PE remains controversial. Studies of younger patients demonstrated that patients with isolated SSPE have a lower prevalence of new/worsening dyspnoea and concomitant DVT [3, 36], lower levels of biomarkers, fewer signs of right-ventricular dysfunction [3], and a lower prevalence of arterial hypoxemia and tachycardia than patients with more proximal PE [3, 37]. Our results could not show that elderly patients with isolated SSPE have a more subtle clinical presentation.

Elderly patients with isolated SSPE and more proximal PE did not differ in terms of VTE risk factors and comorbid conditions in our study, with the exception of a higher cancer prevalence in the SSPE group (28% vs. 15%). The latter may be potentially explained by a lower threshold to perform CTPA in elderly patients with active cancer, thus increasing the rate of detected oligosymptomatic SSPE. Alternatively, the prothrombotic state associated with cancer could result in a greater risk for small, peripheral PE in the elderly.

Our finding that the vast majority of patients with isolated SSPE are managed with anticoagulation treatment is consistent with the results from surveys and other studies [6, 38, 39]. We did not observe a statistically significant difference in the

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duration of initial anticoagulation in patients with SSPE and more proximal PE, demonstrating that physicians do not primarily use the localization of PE to determine the duration of anticoagulant treatment. The higher proportion of outpatient management in patients with SSPE compared with proximal PE (11% vs. 4%) indicates that physicians perceive the risk of adverse outcomes related to SSPE to be lower. The lower proportion of VKA treatment in patients with SSPE is most probably attributable to the higher prevalence of cancer in this group.

We did not find statistically significant differences in recurrent VTE, overall mortality, PE-related mortality, and PE-specific quality of life between patients with isolated SSPE and proximal PE, acknowledging that the number of outcome events was low in our study. The slightly higher 3-year cumulative mortality incidence in patients with SSPE (29% vs. 20%) could be explained with the higher prevalence of cancer in this group. After adjustment for potential confounders, isolated SSPE was not independently associated with a lower risk of clinical outcomes compared to proximal PE. Our results are consistent with a study by den Exter, et al., who did not find statistically significant differences in the 3-month risks of recurrent VTE and overall mortality between anticoagulated patients with isolated SSPE and more proximal PE, although the age of their study population was lower (mean age 56 years) [5]. However, as almost all patients received anticoagulation in our and den Exter's study, outcome comparisons between SSPE vs. proximal PE may be blurred. Interestingly, seven deaths were related to the index PE in the proximal PE group vs. zero in the SSPE group. This finding indicates that case-fatality may not be a direct consequence of SSPE, which is unlikely to cause hemodynamic instability.

A growing body of evidence from retrospective and non-randomized prospective studies suggests that withholding anticoagulation may be as safe as anticoagulant treatment in selected low-risk patients with isolated SSPE [12, 13]. Our study does not

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provide any evidence that isolated SSPE represents a clinically more benign form of PE in the elderly. However, a substantial proportion of patients in our sample had cancer (28%) or concomitant DVT (3%), two well-known risk factors for recurrent VTE [28, 31, 32], and death [16, 18, 33, 34]. Thus, withholding anticoagulation in selected low-risk patients with isolated SSPE, i.e., those without cancer or concomitant DVT, may still be an option but the risk-benefit ratio of such an approach should be examined in a randomized trial before it can be adopted into clinical practice.

Our study has potential limitations. First, as patients were solely enrolled in hospital in- and outpatient services, healthier patients with clinically more benign forms of SSPE who were diagnosed and entirely managed outside the hospital may be underrepresented in our study. Second, as in most studies of SSPE, the diagnosis of isolated SSPE was made by on-site radiologists and was not independently adjudicated [5, 40, 41]. Because the interobserver agreement for SSPE based on CTPA is only fair (k=0.38) [8] and the diagnosis of SSPE based on ventilation/perfusion scanning is not standardized [42], we cannot exclude the possibility that some patients were misclassified as having isolated SSPE in our study. However, when we considered only CTPA-based PEs in a sensitivity analysis, the results did not change markedly, confirming the robustness of our findings. Third, we could not distinguish isolated single from multiple SSPEs, as the number of SSPEs were not documented in our database. As no studies comparing the prognosis of single vs. multiple isolated SSPEs exist, whether patients with single vs. multiple SSPE have differential outcomes, is unknown. Fourth, the assessment of concomitant DVT was not systematic but was left to the discretion of the managing physicians, which must have resulted in an underestimation of the true prevalence of concomitant DVT. Fifth, this study is an ancillary study from the SWITCO65+ cohort and we have not done a power calculation. Thus, the relatively small number of events limits the power to detect

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potential outcome differences between SSPE and more proximal PE. Finally, direct oral anticoagulants (DOACs) were not authorized for treatment of acute VTE during the study recruitment period in Switzerland and it is possible that bleeding rates would be lower if DOACs rather than VKAs had been used [43].

In conclusion, clinical presentations and incidences of adverse outcomes did not differ significantly between elderly patients with SSPE and those with proximal PE, although the power to detect differences might have been limited given the small number of events. Overall, our study does not provide any evidence that unselected, elderly patients with isolated SSPE have a benign clinical course and may not need anticoagulant treatment. Whether withholding anticoagulation in selected low-risk patients with isolated SSPE (e.g., those without cancer or concomitant DVT) is safe, must be examined in a future randomized-controlled trial.

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ADDENDUM

Authorship

N. Stoller, A. Limacher, and D. Aujesky were responsible for study design. A. Limacher did the statistical analyses. N. Stoller and D. Aujesky wrote the manuscript. A. Limacher, M. Méan, C. Baumgartner, T. Tritschler, M. Righini, JH. Beer, and N. Rodondi critically reviewed the manuscript. M. Méan, M. Righini, JH. Beer, N. Rodondi, and D. Aujesky collected data and obtained funding from the Swiss National Science Foundation. All authors had full access to the data and a role in the writing of this manuscript.

Declaration of competing interest

N. Stoller, A. Limacher, M. Méan, C. Baumgartner, M. Righini, N. Rodondi, and D. Aujesky have nothing to disclose. T. Tritschler reports grants from the Swiss National Science Foundation (SNF P2ZHP3_177999), and non-financial support from Pfizer, outside the submitted work. JH. Beer has received research grant support from the Swiss National Science Foundation and from the Swiss Heart Foundation, grant support, lecture and conference fees from Böhringer, Pfizer, Bayer, and Daiichi Sankyo Company. We have no writing assistance to declare.

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519 **FIGURE LEGENDS**

520 **Figure 1.**

521 Patient flow chart.

522

523 **Figure 2.**

524 **a. Aalen-Johansen estimates of recurrent VTE by localization of PE**

525 The 3-year cumulative incidence of recurrent VTE was 7% in patients with isolated
526 SSPE and 12% in patients with more proximal PE (P=0.413 by the Gray-test).

527

528 **b. Kaplan-Meier estimates of overall mortality by localization of PE**

529 The 3-year cumulative incidence of overall mortality was 29% in patients with isolated
530 SSPE and 20% in patients with more proximal PE (P=0.086 by the log-rank test).

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Table 1. Patient baseline characteristics and treatments by localization of PE

	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	
Characteristics[a]	**n (%) or median (interquartile range)**			**P-value**
Baseline characteristics				
Patient age, years	75 (70; 81)	76 (69; 81)	74 (70; 81)	0.85
Male sex	308 (53)	27 (42)	281 (55)	0.06
VTE risk factors				
Active cancer[b]	94 (16)	18 (28)	76 (15)	0.01
Immobilisation[c]	127 (22)	11 (17)	116 (23)	0.33
Major surgery[d]	91 (16)	11 (17)	80 (16)	0.74
Current oestrogen therapy[e]	19 (3)	4 (6)	15 (3)	0.16
History of VTE	155 (27)	15 (23)	140 (27)	0.52
Comorbid conditions				
Chronic heart failure	42 (7)	5 (8)	37 (7)	0.86
Chronic lung disease	93 (16)	14 (22)	79 (15)	0.18
History of major bleeding[f]	64 (11)	6 (9)	58 (11)	0.68
Clinical symptoms & signs of VTE				
Acute chest pain[g]	280 (48)	35 (55)	245 (48)	0.29
New or worsening dyspnoea[g]	472 (82)	47 (73)	425 (83)	0.07
New unilateral leg pain or swelling[g]	129 (22)	17 (27)	112 (22)	0.39
Confirmed distal DVT[h]	28 (5)	2 (3)	26 (5)	0.50
Pulse ≥110/min.	71 (12)	2 (3)	69 (13)	0.02
Systolic BP <100 mm Hg	22 (4)	2 (3)	20 (4)	0.81
Respiratory rate ≥30/min.	20 (3)	0 (0)	20 (4)	0.12
Body temperature <36°C	43 (7)	4 (6)	39 (8)	0.75
Altered mental status[i]	20 (3)	0 (0)	20 (4)	0.11
Arterial O_2 saturation <90%	89 (15)	6 (9)	83 (16)	0.20

(continued)

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Characteristics	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	P-value
	n (%) or median (interquartile range)			
Clinical probability for PE [17]				0.54
Low	98 (17)	9 (14)	89 (17)	-
Intermediate	427 (74)	47 (73)	380 (74)	-
High	53 (9)	8 (13)	45 (9)	-
PESI risk classes [18]				0.51
I	4 (1)	1 (2)	3 (1)	-
II	192 (33)	22 (34)	170 (33)	-
III	177 (31)	18 (28)	159 (31)	-
IV	131 (23)	18 (28)	113 (22)	-
V	74 (13)	5 (8)	69 (13)	-
Diagnostic method				<0.001
Positive spiral CT	520 (90)	47 (73)	473 (92)	-
Pulmonary angiography	2 (0)	1 (2)	1 (0)	-
High-probability ventilation/perfusion lung scintigraphy	56 (10)	16 (25)	40 (8)	-
Laboratory findings				
Hs-cTNT, pg/mL	15 (8; 32)	15 (6; 28)	15 (8; 33)	0.57
NT-proBNP, pg/mL	571 (209; 1566)	547 (272; 1386)	577 (205; 1644)	0.95
D-dimer, ng/mL	2341 (1505; 3560)	2005 (1087; 3651)	2361 (1531; 3545)	0.09
Anemia[j]	221 (38)	28 (44)	193 (38)	0.23
Thrombocytopenia[k]	83 (14)	6 (9)	77 (15)	0.26
VTE-related treatment				
Type of AC started within 1 month of PE				
VKA therapy[l]	518 (90)	51 (80)	467 (91)	0.01
Parenteral AC[m]	564 (98)	61 (95)	503 (98)	0.21

(continued)

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Characteristics	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	P-value
	n (%) or median (interquartile range)			
No initial AC	4 (1)	1 (2)	3 (1)	0.37
Thrombolysis[n]	19 (3)	0 (0)	19 (4)	0.12
Inferior vena cava filter	8 (1)	0 (0)	8 (2)	0.32
Concomitant treatments				
Antiplatelet drugs/NSAIDs[o]	237 (41)	29 (45)	208 (40)	0.46
Outpatient management[p]	28 (5)	7 (11)	21 (4)	0.02

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; VTE= venous thromboembolism; DVT= deep vein thrombosis; BP= blood pressure; CT= computed tomography; Hs-cTNT= high-sensitivity cardiac troponin T; VKA= vitamin K antagonists; AC= anticoagulation; NSAID= non-steroidal anti-inflammatory drugs.

[a]Data were missing for pulse (1%), systolic BP (1%), respiratory rate (22%), body temperature (2%), arterial O_2 saturation (6%), Hs-cTNT (13%), NT-proBNP (13%), D-dimer (15%), anemia (2%), and thrombocytopenia (2%).

[b]Solid or hematologic cancer requiring chemotherapy, radiotherapy, surgery, or palliative care during the last 3 months.

[c]Bed rest >72 hours, voyage in sitting position for >6 hours, fracture or cast of the lower extremity during the last 3 months.

[d]Surgery requiring general or spinal anaesthesia during the last 3 months.

[e]Any oestrogen-containing treatment such as osteoporosis prevention/treatment, oral hormone replacement therapy, or antitumor treatment for breast or prostate cancer during the last 3 months.

[f]History of a symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in haemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units of whole blood or red cells [44].

[g]During the last 21 days.

[h]Confirmed by compression ultrasonography or contrast venography.

[i]Disorientation, lethargy, stupor, or coma.

[j]Haemoglobin <13 g/dL in men or <12 g/dL in women.

[k]Platelet count <150 G/L.

[l]Acenocoumarol or phenprocoumon.

[m]Intravenous or subcutaneous unfractionated heparin, dalteparin, enoxaparin, nadroparin, fondaparinux, or other.

[n]Systemic or catheter-directed thrombolysis.

[o]Aspirin, clopidogrel, prasugrel, aspirin/dipyridamol, or any NSAID (e.g., ibuprofen).

[p]Hospital stay for <24 hours.

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Table 2. Clinical outcomes by localization of PE

Clinical outcomes	All (N=578)	Isolated SSPE (N=64)	Proximal PE (N=514)	P-value
	n (%)			
Recurrent VTE				
At 3 months	7 (1)	1 (2)	6 (1)	0.56
Entire follow-up period	59 (10)	5 (8)	54 (11)	0.66
Recurrent PE				
At 3 months	6 (1)	1 (2)	5 (1)	0.51
Entire follow-up period	45 (8)	3 (5)	42 (8)	0.46
Recurrent DVT				
At 3 months	1 (0)	0 (0)	1 (0)	1.00
Entire follow-up period	17 (3)	2 (3)	15 (3)	1.00
Overall mortality				
At 3 months	31 (5)	7 (11)	24 (5)	0.07
Entire follow-up period	115 (20)	18 (28)	97 (19)	0.10
Definite or possible PE-related death				
During the index hospitalization	7 (1)	0 (0)	7 (1)	1.00
At 3 months	11 (2)	1 (2)[a]	10 (2)[b]	1.00
Entire follow-up period	23 (4)	2 (3)[c]	21 (4)[d]	0.52

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; VTE= venous thromboembolism; DVT= deep vein thrombosis.

[a]Cause of death was adjudicated as possibly related to PE.

[b]Cause of death was adjudicated as definitely due to PE in 3 patients and as possibly related to PE in 7 patients.

[c]Cause of death was adjudicated as possibly related to PE in both patients.

[d]Cause of death was adjudicated as definitely due to PE in 6 patients and as possibly related to PE in 15 patients.

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Table 3. Association between localization of PE and VTE recurrence or overall mortality

	All PE diagnosis (N=578)	CTPA-based PE diagnosis only (N=520)
	Adjusted sub-hazard ratio (95%CI)	
VTE recurrence		
Proximal PE	Reference	Reference
Isolated SSPE	0.64 (0.25–1.62)[a]	0.57 (0.20–1.62)[a]
	Adjusted hazard ratio (95%CI)	
Overall mortality		
Proximal PE	Reference	Reference
Isolated SSPE	1.12 (0.64–1.96)[c]	1.34 (0.71–2.53)[c]

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; CTPA= computed tomography pulmonary angiography; CI= confidence interval; VTE= venous thromboembolism.

[a]Adjusted for age, sex, active cancer, prior VTE, and periods of anticoagulation as a time-varying covariate.

[b]Adjusted for age, sex, previous major bleeding, active cancer, low physical activity, anemia, thrombocytopenia, antiplatelet or non-steroidal anti-inflammatory drugs, and periods of anticoagulation as a time-varying covariate.

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Table 4. Duration of anticoagulation by localization of PE

	All (N=527)[a]	Isolated SSPE (N=56)	Proximal PE (N=471)	
	n (%) or median (interquartile range)			P-value
Duration of initial AC, months	12.2 (6.2; 28.0)	10.7 (6.1; 24.1)	12.3 (6.3; 28.7)	0.34
Duration of initial AC				0.35
≤3 months	38 (7)	7 (13)	31 (7)	-
3–6 months	74 (14)	6 (11)	68 (14)	-
6–12 months	147 (28)	17 (30)	130 (28)	-
>12 months	268 (51)	26 (46)	242 (51)	-

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; AC= anticoagulation.

[a]Patients who died within the first 6 months were excluded from this analysis (N=51).

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Table 5. Quality of oral anticoagulant by localization of PE

INR range[a]	All (N=494)	Isolated SSPE (N=48)	Proximal PE (N=446)	
	median % of time (interquartile range)			P-value
2.0–3.0	65.1 (48.1; 80.5)	66.4 (45.3; 82.2)	65.0 (48.1; 80.5)	0.71
>3.0	10.4 (3.1; 20.5)	11.4 (3.2; 20.3)	10.3 (3.1; 20.6)	0.91
<2.0	15.7 (6.3; 33.3)	15.5 (3.9; 30.6)	15.7 (6.6; 33.5)	0.55

Abbreviations: (SS)PE= (subsegmental) pulmonary embolism; INR= international normalized ratio.
[a]Only patients with initial vitamin K antagonist treatment and at least two INR measurements were considered.

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Figure 1.

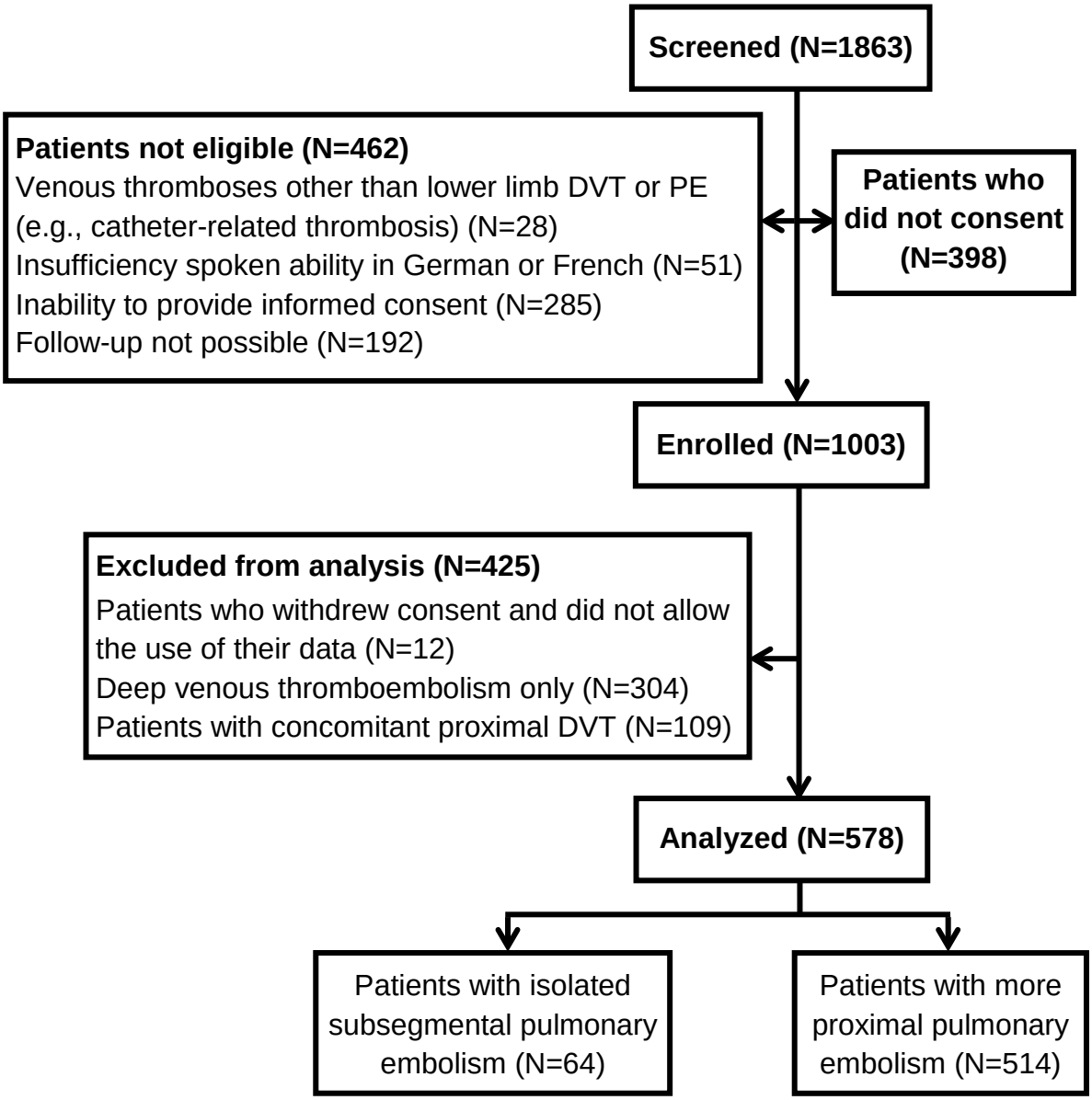

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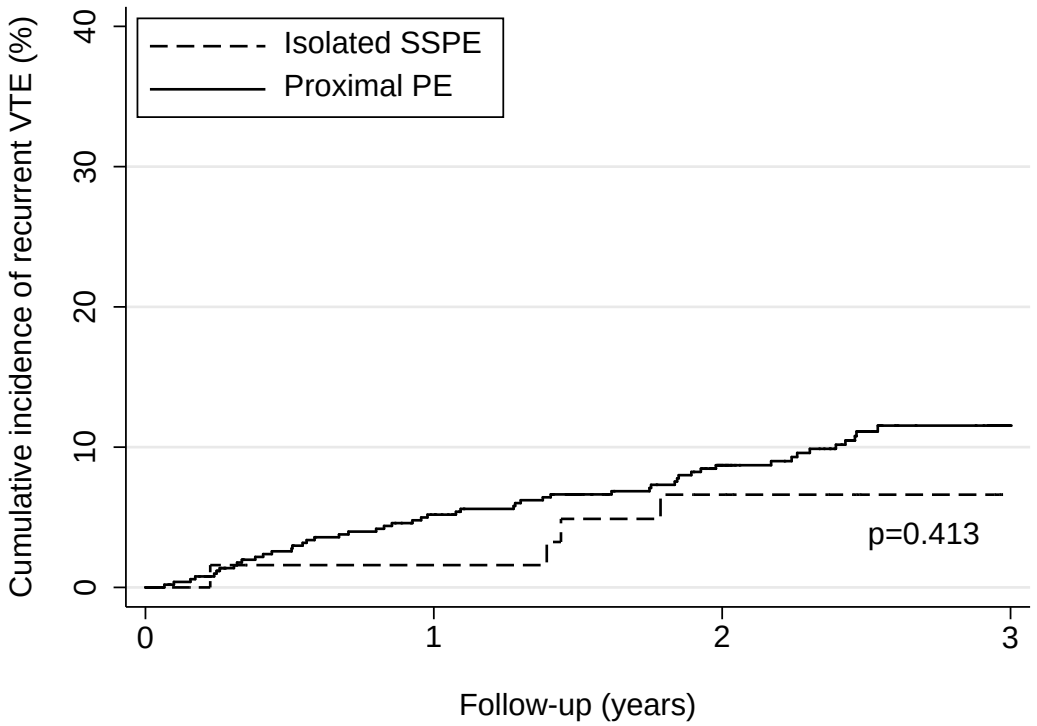
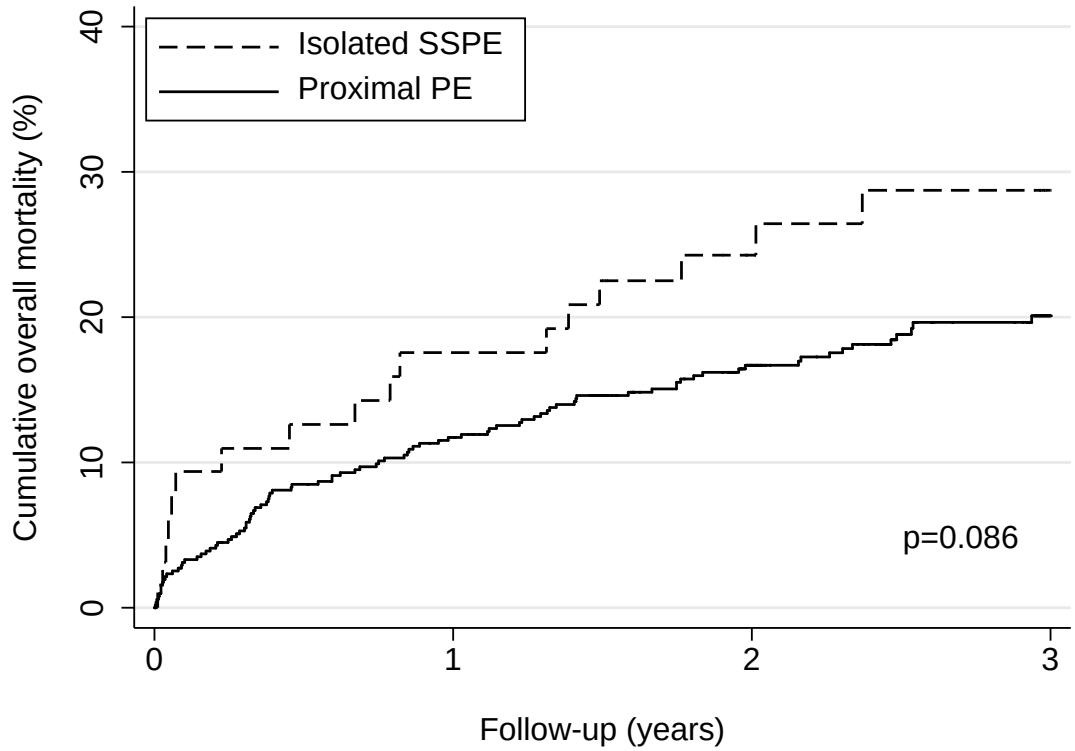
Figure 2.

a)



Number at risk				
Isolated SSPE	64	60	35	16
Proximal PE	514	467	337	114

b)



Number at risk				
Isolated SSPE	64	50	37	17
Proximal PE	514	435	314	131